



Fred Lembeck (1922-2014)

A pharmacologist who discovered serotonin in carcinoids and pioneered research on substance P.

„It will probably always be more important to try a thing out than to argue about it.“ This bon-mot by Sir John Henry Gaddum can rightly be seen as a guiding motto in Fred Lembeck’s scientific endeavours. Besides John Gaddum, it was also Ulf

Svante von Euler, Sir Henry Hallet Dale and Otto Loewi who stood as models and peers to navigate Fred Lembeck into the pharmacology of neurotransmitters and neuropeptides. Fred was a successor of Otto Loewi on the chair of pharmacology at the University of Graz in Austria and throughout his life fascinated by the scientific achievements of this 1936 Nobel Laureate. No wonder, that the legacy of Otto Loewi lives on not only in Fred Lembeck’s movie and book on Otto Loewi (Lembeck and Giere, 1968) but also in his scientific advances. Fred continued to work in the laboratory until his eighties and passed away on 22 October 2014 at the age of 92, survived by his daughter Eva Désirée and his sons Klaus and Andreas.

Fred Lembeck had been born on 4 July 1922 in Oberwinden, a small village near Herzogenburg in Lower Austria. His destination in pharmacology was not at all clear in 1947 when he graduated as M.D. after studying medicine in Vienna and Graz during and after the bleak war times, interrupted by service as army doctor and being caught as a prisoner of war. As he writes, “I spent only 3 years and 3 months as a real student ... and when I received my degree I sincerely wished I had had the money to stay for another year in order to acquire more knowledge” (Lembeck, 1980). Nevertheless, by a lucky incidence, he was able to join the Department of Pharmacology at the University of Graz as a tutor soon after his graduation. It was even more fortunate that an official of the World Health Organization, visiting Graz at that time, was taken to Professor Hans F. Häusler, the head of department and only English-speaking professor of the Medical Faculty. Hans Häusler persuaded the official to offer Fred a fellowship to work with John Gaddum in Edinburgh, which led Fred to recall: “My arrival there, 1 year after my graduation, was my entrance into pharmacology and decisive for the rest of my life” (Donnerer and Lembeck, 2006).

Back in Graz from Edinburgh where he had focused on the pharmacology of noradrenaline, Fred turned to two bioactive compounds which he had also encountered in John Gaddum’s laboratory: serotonin and substance P. Serotonin had just been found in enterochromaffin cells of the gut by Vittorio Erspamer, when Fred discovered it to occur in carcinoid tumours, using chromatographic methods and bioassays he had learned to perform in Edinburgh (Lembeck, 1953a). In the same year he also published a seminal paper on substance P (Lembeck, 1953b), another bioactive but even more enigmatic compound that Ulf von Euler and John Gaddum had discovered back in 1931. In his work, Fred demonstrated that the concentration of substance P in the dorsal roots of the spinal cord was much higher than in the ventral roots and concluded that substance P might be a transmitter of primary afferent neurons (Lembeck, 1953b). This suggestion had to wait for another 25 years until it was confirmed by immunohistochemical and other methods following the identification of substance P as an undecapeptide. The 1953 paper is also particularly remarkable with regard to its emergence from the last experiment Otto Loewi performed in Graz before he fell victim to the Nazi racism and was put into prison in 1938 (Fred Lembeck – Wikipedia).

Just before the takeover of Austria by the Nazis, Otto Loewi had found that acetylcholine is apparently absent from the dorsal roots of the spinal cord. Already in prison, Otto

Loewi managed to obtain a pencil and to send a post card to the Springer Verlag in Berlin, in which he briefly described the results and asked for their publication. Fortunately, this card fell into the hands of Paul Rosbaud (born 1896 in Graz, then a consultant of Springer Verlag and spy for England, later founder of Pergamon Press) who immediately forwarded the card to Henry Dale for communication to the Physiological Society (Loewi and Hellauer, 1938). After the war, Horst F. Hellauer (the former assistant of Otto Loewi) and Karl Umrath confirmed that the dorsal roots lacked acetylcholine but contained a vasodilator compound that was neither acetylcholine nor histamine. Fred Lembeck stepped in and showed that this compound could be substance P, dedicating his paper to Otto Loewi on the occasion of his 80th birthday (Lembeck, 1953b).

In 1954, Fred was promoted to Dozent (Lecturer) at the Department of Pharmacology of the University of Graz, and in 1961 he moved to Germany to become Professor and Head of the Department of Pharmacology at the University of Tübingen. Here, Fred Lembeck and Klaus Starke discovered that substance P enhances vascular permeability (Lembeck and Starke, 1963) and characterized the effect of substance P and related peptides, termed tachykinins by Vittorio Erspamer, to stimulate the secretion of saliva (Lembeck and Starke, 1968). The discovery of the sialogogic action of substance P contributed, though *indirectly*, to the isolation and identification of substance P as the undecapeptide we know today. Reading the newspaper "Frankfurter Allgemeine Zeitung" in an Intercity train, Fred stumbled over a short note saying that researchers at Brandeis University in the US had discovered a sialogogic factor in the hypothalamus (Lembeck, 2008). Back in office, Fred immediately got in touch with Susan E. Leeman, the lead author at Brandeis University, and the further exchange between the two soon convinced Susan Leeman that the sialogogic factor she had discovered was identical to substance P. The amino acid sequence of substance P was published in 1971 (Chang et al., 1971).

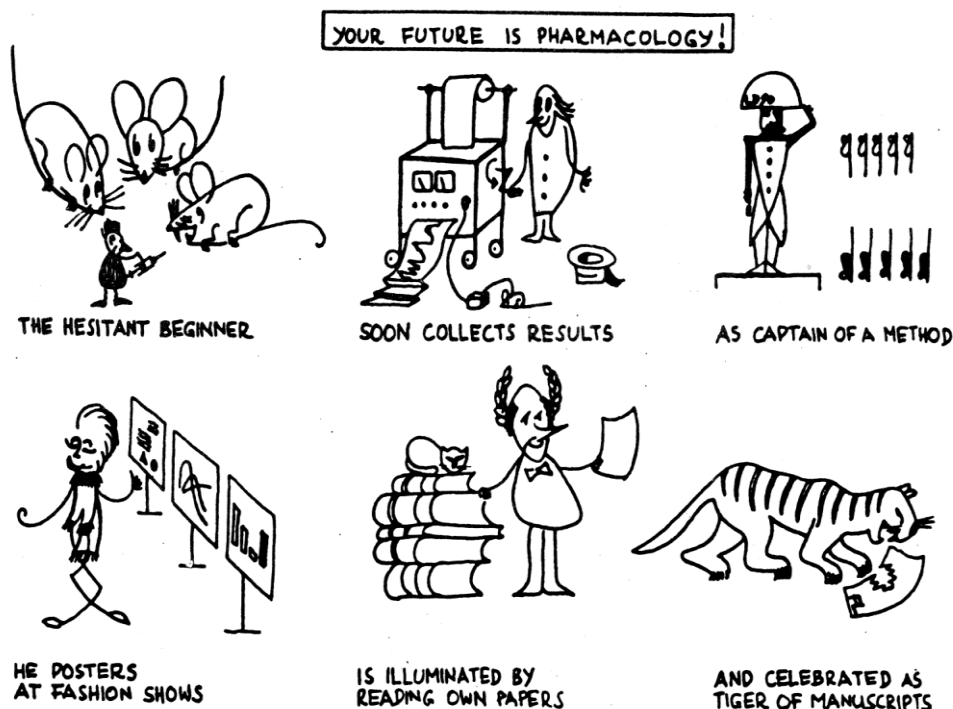
In 1969 Fred Lembeck returned to Graz to become Professor and Head of the department (renamed to Department of Experimental and Clinical Pharmacology) in which his career in pharmacology had begun in 1947. His second term in Graz up to his retirement in 1992 proved to be another enormously fruitful period in which the department became internationally recognized for its contributions to neuropeptide research and sensory neuropharmacology. The scope of the work was considerably expanded, focussing on several aspects of substance P and other peptides (including bradykinin) in cutaneous, gastrointestinal, pulmonary and urogenital physiology and pharmacology, neurogenic inflammation, pain and various aspects of autonomic neuropharmacology. Exploiting the advent of tachykinin and bradykinin receptor antagonists, Fred was eager to provide pharmacological evidence for the implications of substance P and bradykinin in health and disease and to explore substance P and bradykinin receptors as potential targets for therapy.

Since the late 1970s, Fred Lembeck and his group took use of a pharmacological tool that exhibited a remarkable selectivity for peptidergic sensory neurons: capsaicin (Holzer, 1991). Part of this research was conducted in close collaboration with colleagues in Hungary (Gábor Jancsó, János Szolcsányi, Loránd Barthó), given that the selective action of capsaicin on sensory neurons had been originally discovered by the Hungarian pharmacologist Nikolaus (Miklós) Jancsó. By utilizing capsaicin's acutely excitatory and long-term desensitizing actions, the multiple implications of sensory neurons in sensation, pain, vascular function and autonomic regulation were systematically mapped (Lembeck and Holzer, 1979; Gamse et al. 1980). These studies also revealed that capsaicin's action is not selective for a particular neuropeptide phenotype of sensory neurons, but extends to a range of capsaicin-sensitive neurons that were later characterized to express transient receptor potential channels of the vanilloid type 1 (TRPV1), the molecular target of capsaicin.

Research was the lifeblood in Fred Lembeck's career. As alluded to above, he pursued a hands-on approach, being equally keen on the intellectual plan of an experiment and the design of the protocol and equipment required. Despite this predilection, he liked every

aspect of his profession, was a keen teacher (Lembeck, 1980), and wrote books to promote the practical aspects of pharmacology, such as "Prescription 101" (in German and Greek, 8 editions), "Pharmacological facts and figures" (in English, German and Japanese, 4 editions) and "Practical course in pharmacology" (in German, 1 edition). His enormous knowledge led him to write commentaries on a wide range of topics in professional newsletters as well as newspapers and to take an active part in university, health and research politics. Even when the Medical Faculty was transformed into the independent Medical University of Graz in 2004, he actively participated in the discussion as to how the new university should be shaped. Fred was President of the German Society of Pharmacology and Toxicology, served 1972-1975 as General Secretary of the International Union of Pharmacology (IUPHAR), and invested much effort in turning Naunyn-Schmiedeberg's Archives of Pharmacology into an international journal published exclusively in English (Fred Lembeck – Wikipedia).

Fred Lembeck was a pioneer in his field of research, and his achievements were recognized by many national and international honours and awards, only a few of which are listed here. He was elected honorary member of many pharmacological societies including the Hungarian Pharmacological Society (1979), the German Society of Experimental and Clinical Pharmacology and Toxicology (1988), the Austrian Pharmacological Society (2001) and the British Pharmacological Society (2007). He was a member of the Deutsche Akademie der Naturforscher Leopoldina (1983), a corresponding member of the Austrian Academy of Sciences (1988) and a founding member of the Academia Europaea (1988). In 1985 he was awarded the Oscar Gans Prize of the German Society of Dermatology and the Oswald Schmiedeberg Medal of the German Society of Experimental and Clinical Pharmacology and Toxicology, in 2001 named as Highly Cited Author in Pharmacology, and in 2007 decorated with the Austrian Cross of Honour for Science and Art.



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Despite his many recognitions, Fred Lembeck was a modest and self-effacing person, yet at any rate passionate to thrill his contemporaries inside and outside the department by his excitement about research. He led the department by setting an example of a devoted scientist, and this spark of enthusiasm quickly caught up with the other members of the group. When young researchers proved promising and successful they

were consistently mentored by Fred, and many of them made a distinguished career in academia, pharmaceutical industry or regulatory body. Fred knew that good science requires a stimulating atmosphere in the laboratory including mentorship, openness for new developments and discoveries, sufficient funding, successful publication, international mobility and proper recognition. At the same time, and as his sketch on "Your future is pharmacology" vividly shows, he was also well aware of the downsides of the scientific profession. Although being an ardent scientist, Fred Lembeck pursued many interests that went far beyond science but had an important impact on his professional life. He was extremely knowledgeable about the history of science, and was most entertaining when he narrated stories from the archives of physiology and pharmacology. He also loved music and enjoyed hiking in the mountains, photographing as well as drawing. In so doing Fred considerably expanded John Gaddum's definition of a pharmacologist as "the 'jack of all trades' borrowing from physiology, biochemistry, pathology, microbiology and statistics".

**Professor Peter Holzer, FBPharmacols
Institute of Experimental and Clinical Pharmacology
Medical University of Graz
e-mail: peter.holzer@medunigraz.at**

References

- Chang MM, Leeman SE, Niall HD (1971). Amino-acid sequence of substance P. *Nat New Biol* 232:86-87.
- Donnerer J, Lembeck F (2006). *The Chemical Languages of the Nervous System*. Karger: Basel.
- Fred Lembeck – Wikipedia. [Online] Available from http://de.wikipedia.org/wiki/Fred_Lembeck [Accessed: 14th December 2014].
- Gamse R, Holzer P, Lembeck F (1980). Decrease of substance P in primary afferent neurones and impairment of neurogenic plasma extravasation by capsaicin. *Br J Pharmacol* 68: 207-213.
- Holzer P (1991). Capsaicin: cellular targets, mechanisms of action, and selectivity for thin sensory neurons. *Pharmacol Rev* 43: 143-201.
- Lembeck F (1953a). 5-Hydroxytryptamine in a carcinoid tumour. *Nature* 172: 910-911.
- Lembeck F (1953b). Zur Frage der zentralen Übertragung afferenter Impulse. III. Mitteilung. Das Vorkommen und die Bedeutung der Substanz P in den dorsalen Wurzeln des Rückenmarks [Central transmission of afferent impulses. III. Incidence and significance of the substance P in the dorsal roots of the spinal cord]. *Naunyn-Schmiedeberg's Arch Exp Pathol Pharmacol* 219: 197-213.
- Lembeck F (1980). Teaching in pharmacology (the old-fashioned method). *Trends Pharmacol Sci* 1:I-II.
- Lembeck F (2008). The archeology of substance P. *Neuropeptides* 42: 444-453.
- Lembeck F, Giere W (1968). *Otto Loewi. Ein Lebensbild in Dokumenten*. Springer-Verlag: Berlin, Heidelberg, New York.
- Lembeck F, Holzer P (1979). Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. *Naunyn-Schmiedeberg's Arch Pharmacol* 310: 175-183.
- Lembeck F, Starke K (1963). Substance P content and effect on capillary permeability of extracts of various parts of human brain. *Nature* 199: 1295-1296.
- Lembeck F, Starke K (1968). Substanz P und Speichelsekretion [Substance P and salivary secretion]. *Naunyn-Schmiedeberg's Arch Exp Pathol Pharmacol* 259: 375-385.
- Loewi O, Hellauer H (1938). The acetylcholine content of the nerves of warmblooded animals. *J Physiol (London)* 93: 34P.